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**REMARKS**

Claims 1-14, 17, 18, 21, 23 and 27, 28 and 30-37 and 40-42 are pending in the application. Claims 3-13 and 33-37 have been previously withdrawn. Claim 40 was withdrawn by the Examiner. Claims 16, 19, 20, 22, 24-26 have been cancelled previously. Claims 15, 29, 38-39 have now been cancelled.

**Status of the claims**

The Examiner confirms that claims 1, 2, 14, 15, 17, 18, 21, 23, 27-32, 38 and 39-42 are under examination. The Examiner further mentions that claim 40 contains numerous distinct inventions and is therefore withdrawn from consideration. In this regard, the Applicants respectfully disagree with the Examiner since claim 40 is directed to specific oligonucleotide sequences. Nowhere during the prosecution has the Examiner requested election of a specific sequence or restricting the present invention to a specific oligonucleotide. To the contrary, following election of Group II of invention in the response to the Restriction Requirement dated March 10, 2006, the Examiner should have searched for any nucleotide sequence of at least 10 nucleotides in length, which has an antiviral activity against RSV or parainfluenza virus infection, wherein said antiviral activity occurs principally by a non-sequence complementary mode of action. It is incomprehensible that now the Examiner is of a different opinion since in the first restriction requirement issued March 10, 2006, no such election of a specific oligonucleotide was required. Consequently, even after issuing the restriction requirement and further prosecution of the present application, the Examiner is backtracking. Thus, it is believed that by further specifying the sequences of the oligonucleotide in claim 40, it does not impose any burden for a new search by the Examiner. Reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

**Claim rejections - 35 U.S.C. § 112**

Claims 1, 2, 14, 15, 17, 18, 21, 23, 27-32, 38, 39, 41 and 42 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirements. The Examiner mentions that the claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. More

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specifically, the Examiner is of the opinion that the specification does not enable the prophylaxis or treatment of a RSV or parainfluenza virus infection in a subject comprising administering to a subject in need of such treatment a therapeutically effective amount of at least one pharmacologically-acceptable oligonucleotide of at least 10 nucleotides in length. In her opinion, the specification does not disclose treatment of a virus infection with one oligonucleotide. The Examiner mentions that the claimed invention is drawn to a method of prophylaxis or treatment of a RSV or parainfluenza virus infection in a subject by administering random sequence oligonucleotides that have antiviral activity. The Examiner also mentions that the art (Peyman *et al.*) also teaches that a population of randomers can exhibit antiviral activity, and acknowledges that it does not illustrate a single oligonucleotide effective as an antiviral agent. Consequently, the Examiner requests that detailed teachings are required in the disclosure to enable the full scope of the claims. More specifically, the Examiner mentions that only examples are provided for randomers of approximately 25 nucleotides in length. However, no examples are provided for one oligonucleotide.

In this regard, the Applicants wish to first submit that claim 1 was amended to replace the expression “at least one pharmacologically acceptable oligonucleotide” by “a pharmacological acceptable oligonucleotide”. Consequently, it is believed that the expression “at least one pharmacologically acceptable oligonucleotide” which was causing problem in view of the examiner’s comments has been deleted. Further, claim 1 was amended to define that the encompassed oligonucleotide is of at least 20 nucleotides in length and that said oligonucleotide is not complementary to any portion of the genomic sequence of RSV or parainfluenza virus. Claims 15 and 29 have been deleted in order to avoid any redundancy and contradiction with claim 1. Furthermore, it is respectfully pointed out to the Examiner that Figures 25a-c of the present description clearly demonstrate that randomers of 20, 40 and 80 nucleotides in length have an anti-RSV activity *in vitro*. Furthermore, on September 28, 2006, a declaration by Dr. Jean-Marc Juteau was submitted wherein results were provided for the effectiveness of REP 2006 (randomer of 40 nucleotide in length) in order to inhibit RSV infection in a cotton rat model. Result demonstrating the efficacy of REP 2006 to inhibit parainfluenza-3 virus infection are recited in Example 8 in the present description. Consequently, the results presented in the description and in the declaration submitted on September 28, 2006, are enabling for a method for the prophylaxis or treatment of a RSV or parainfluenza virus infection in a subject by administering a pharmacological acceptable

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oligonucleotide of at least 20 nucleotides in length, wherein said oligonucleotide comprises at least one phosphorothioated linkage, is not complementary to any portion of the genomic sequence and to an mRNA sequence of RSV or parainfluenza virus and wherein the anti-viral activity of said oligonucleotide occurs principally by a non-sequence complementary mode of action.

Regarding the Examiner's comment that Peyman *et al.* teaches that a population of randomers can exhibit antiviral activity, the Applicants wishes to specify that Peyman *et al.* only teaches that antisense oligonucleotides have antiviral activity. Peyman *et al.* is only enabled for four antisense oligonucleotides against HSV-1 in cell culture (as disclosed in column 14, lines 14-19 in Peyman). In fact, Peyman *et al.* were not at all concerned with identifying antiviral oligonucleotides sequences, but only with improving known antisenses by stabilizing them and improving their cell penetration by capping oligonucleotides (with the addition of a cap of guanine at their extremities). When considering the sequences disclosed by Peyman *et al.*, all of the sequences disclosed therein are antisenses. Moreover, Peyman *et al.*, in column 6, lines 8-9, teaches that the "*effective oligonucleotides are understood to mean antisense oligonucleotides*". By definition, an "antisense" is a molecule that interacts with complementary strands of nucleic acids, modifying the expression of genes. Consequently, a person skilled in the art would recognize that an antisense RNA or single-stranded antisense DNA is a molecule which is complementary to the nucleic acid sequence of a gene of interest. Thus, the mechanism of action of an antisense is sequence dependent since it must be complementary to a strand of nucleic acids in order to interact and modify the expression of the gene of interest. In addition, such person skilled in the art would conclude that SEQ ID NOs: 1-34 in Peyman *et al.* represent sequences that are complementary to a known gene, and thus represent antisense oligonucleotides. The following Table identifies the gene targeted by these antisenses:

Patent Seq ID	Sequence	Homologous to (% coverage)	Accession #
1	ACACCCAATTCTGAAAATGG	HIV-1, complete genome (100)	AF003819.3
2	AGGTCCCTGTTGGCGGCCA	HIV-1 proviral DNA, complete genome (100)	AB289588.1
3	GTCGACACCCAATTCTGAAAATGGATAA	HIV-1, complete genome (100)	AF003819.3
4	GCTATGTCGACACCCAATTCTGA AA	HIV-1 proviral DNA, complete genome (100)	AB287367.1
5	GTCGCTGTCTCCGCTCTCTTC CTG	HIV-1 isolate B055AA from USA tat protein (tat) gene, partial cds (100 [bases 1-22])	AY734162.1
6	GTCTCCGCTTCTTCCTGCCATTAGG	HIV-1 proviral DNA, complete genome (100 [bases 10-27])	AB289588.1

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Patent Seq ID	Sequence	Homologous to (% coverage)	Accession #
7	GCGGGGCTCCATGGGGGTCG	Human herpesvirus 1 complete genome (100)	X14112.1
8	CAGCTGCAACCCAGC	Homo sapiens angiominotin like 1 (AMOTL1), mRNA (100)	NM_130847.2
9	GGCTGCTGGAGCGGGGCACAC	Homo sapiens MYC gene for c-myc proto-oncogene and ORF1 (100)	X00364.2
10	AACGTTGAGGGGCAT	Homo sapiens v-myc myelocytomatosis viral oncogen homolog (100)	NM_002467.3
11	GTGCCGGGGCTTCGGGC	Homo sapiens mRNA for v-myb myeloblastosis viral oncogene (100)	AJ616235.1
12	GGAGAACATCATGGTCGAAAG	Mouse c-fos oncogene (100)	V00727.1
13	CCCGAGAACATCATGGTCGAAG	Mouse c-fos oncogene (100)	V00727.1
14	GGGGAAAGCCCGGCAAGGGG	Mouse c-fos oncogene (100)	V00727.1
15	CACCCGCCTTGGCCTCCAC	Multiple human genomic hits (100)	
16	GGGACTCCGGCGCAGCGC	Human mRNA for precursor of epidermal growth factor receptor (100)	X00588.1
17	GGCAAACTTCTTCTCCTCC	Homo sapiens epidermal growth factor receptor (100)	NM_201284.1
18	GGGAAGGAGGAGGATGAGG	Mus musculus mRNA for p53, complete cds (100)	AB020317.1
19	GGCAGTCATCCAGCTTCGGAG	Mouse mRNA for transformation associated protein p53 (100)	X00741.1
20	GCAGTAAGCATCCATATC	Felis catus integrin beta 1 (100)	NM_001048160.1
21	CCCCCACCACTTCCCCCTCTC	Homo sapiens intercellular adhesion molecule 1 (100)	BC015969.2
22	CTCCCCCACCACTTCCCCCTC	Homo sapiens intercellular adhesion molecule 1 (100)	BC015969.2
23	GCTGGGAGCCATAGCGAGG	Homo sapiens intercellular adhesion molecule 1 (100)	BC015969.2
24	ACTGCTGCCCTTGCTCTCAGG	Homo sapiens HES2 gene (100 [bases 2-16] and multiple genomic hits (100)	NM_019089.3
25	CAATCAATGACTTCAAGAGTT	Homo sapiens selectin E (endothelial) adhesion molecule 1 [bases 7-22] and multiple genomic hits (100)	NM_000450.1
26	GGTCCCTGTTGGCGCCA	HIV-1 proviral DNA, complete genome (100)	AB289588.1
27	GTGCCGGGGCTTCGGG	Homo sapiens mRNA for v-myb myeloblastosis viral oncogene (100)	AJ616235.1
28	GGAGGATGCTGAGGAGG	Human herpesvirus 1 gene for DNA polymerase UL30 (100)	AB231460.1
29	GGAGGATGCTGAGG	Human herpesvirus 1 gene for DNA polymerase UL30 (100)	AB231460.1
30	CAGGAGGATGCTGAGGAGG	Human herpesvirus 1 gene for DNA polymerase UL30 (100)	AB231460.1
31	GGCTGCCATGGTCCC	Homo sapiens fibroblast growth factor 2 (100)	NM_002006.3
32	TCATGGTGTCCCTTGCAGCC	Homo sapiens procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3 (100 [bases 1-15] and multiple genomic hits (100)	NM_001084.4
33	TCATGGTGTCCCTTGCAG	Homo sapiens procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3 (100 [bases 1-15] and multiple genomic hits (100)	NM_001084.4
34	AAGTTCATGGTTTCGG	Homo sapiens vascular endothelial growth factor A (100)	NM_003376.4

In column 6, lines 30-31; column 8, lines 29-30; column 10, lines 35-36; column 11, lines 4-5; and column 14, lines 14-19 of Peyman *et al.*, it is clearly stated that the following oligonucleotides are examples of a novel antisense effective against the following targets:

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SEQ ID NOs	Target gene
35-46	HIV
47-54	HSV-1
55-56	c-Ha-ras
57-60	c-myc
61-63	c-myb
64-70	c-fos
71-72	p120
73-77	EGF receptor
78-81	p53 tumor suppressor
82-83	bFGF
84	VEGF
85-86	VLA-4
87-94	ICAM
95-98	ELAM-1
99-103	TNF-alpha
104-105	HSV-1

Consequently, SEQ ID NOs: 1-105 all represent antisense oligonucleotides which are complementary to a portion of the nucleic acid sequence of a specific gene. Thus, by its inherent properties, as well as by definition, an antisense will modify the expression of a gene by a sequence dependent and complementary mode of action. The present application teaches oligonucleotides having a non-sequence complementary mode of action. For example, with randomer oligonucleotides, as taught in the present description, due to the nature of the preparation used to produce them, a sequence complementary mode of action cannot occur. On page 34 of the present description, it is clearly disclosed that for a randomer oligonucleotide of 40 bases in length, any particular sequence in the population would theoretically represent only  $1/4^{40}$  or  $8.27 \times 10^{-25}$  of the total fraction. Given that 1 mole =  $6.022 \times 10^{23}$  molecules, and the fact that the largest synthesis is currently done on a 15 micromole scale, all possible sequences will not be present. Also, there is most probably only one copy of each sequence. Consequently, by its inherent properties, the mode of action of these oligonucleotides is sequence independent and does not require complementarity to the nucleic acid sequence of a gene. Thus, Peyman *et al.*, or any other prior art, teaches that the antiviral activity of an oligonucleotide not complementary to any portion of the genomic sequence of RSV or parainfluenza virus, occurs by a non-sequence complementary mode of action. Reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

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Claims 1, 2, 14, 15, 17, 18, 21, 23, 27-32, 38, 39, and 41 and 42 have been rejected under 35 U.S.C. 112, first paragraph, for allegedly containing subject matter which was not described in the specification. The Examiner mentions that the language of the claims indicates that these claims are drawn to a genus which is at least one pharmacological oligonucleotide of at least 10 nucleotides in length. She mentions that to provide an adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The Examiner is of the opinion that there is only a single species of the claimed genus disclosed that is within the scope of the claimed genus which is a randomer oligonucleotide corresponding to a few copies of any particular sequence in a preparation, of at least 10 nucleotides in length. In this regard, the Applicants wish to reiterate that in Example 5, an anti-RSV activity is demonstrated for randomer oligonucleotides of at least 20, 40 and 80 paces (REP 2004, REP 2006, and REP 2007; see Figures 25a-c). Furthermore, in Example 8, inhibition of parainfluenza-3 virus is demonstrated for REP 2006. In addition, on September 28, 2006, a declaration by Dr. Jean-Marc Juteau was submitted wherein results were provided for the effectiveness of REP 2006 (randomer of 40 nucleotide in length) in order to inhibit RSV infection in a cotton rat model. In addition, the Applicants also wish to explain that the oligonucleotides used in the present invention can be randomers oligonucleotides. It is believed that a person skilled in the art would acknowledge that because randomer oligonucleotides were efficient to inhibit viral infection, any sequence can also inhibit viral infection since the activity of the encompassed oligonucleotides is independent on the nature of the sequence of said oligonucleotides. The Applicants deliberately choose to exemplify results using randomers nucleotides to avoid being restricted to a specific sequence and to demonstrate that it would work with any sequence as the activity occurs by a sequence independent mode of action. Consequently, it is believed that the present specification provides an adequate written description for a claimed genus which is an oligonucleotide of at least 20 nucleotides in length, as now claimed in the set of claims submitted herewith, having an antiviral activity occurring by a non-sequence complementary mode of action. Reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

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Claim rejections - 35 U.S.C. § 103(a)

Claims 1, 2, 14, 15, 17, 18, 21, 23, 27-32, 38 and 39 have been rejected under 35 U.S.C. 103(a) as allegedly being obvious in view of the teachings of Peyman *et al.* and Milligan *et al.* The Examiner mentions that Peyman *et al.* discloses oligonucleotides where a nucleotide sequence is from 10-40 nucleotides in length, and that these new oligonucleotides are used to treat diseases caused by viruses. The Examiner reiterates her opinion that Peyman teaches sense nucleotides as well as antisense oligonucleotides. While the antisense would be complementary, no part of the sense would be complementary to any part of the viral genome. However, the Examiner acknowledges that Peyman does not teach that sense oligonucleotides have antiviral activity against viruses. In addition, the Examiner mentions that the reference of Milligan *et al.* teach about sense oligonucleotides and antisense oligonucleotides and their ability as potential antiviral applications. The Examiner also mentions that Milligan *et al.* teach that in a study, sense oligonucleotides had a greater antiproliferative effect than antisense oligonucleotides, indicating that a non-antisense mechanism may be responsible for the antiproliferative effect. Consequently, the Examiner is of the opinion that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to use the sense oligonucleotides, as taught by Milligan, to treat RSV or parainfluenza infection with the composition taught by Peyman. The Examiner further specifies that is not recited in the body of the claims that the oligonucleotides of the present invention are not antisense.

Firstly, the Applicants submit that claim 1 has now been amended to define that not only does the anti-viral activity of the recited oligonucleotides occur by a non-sequence complementary mode of action, but that said oligonucleotides are not complementary to any portion of the genomic sequence and to an mRNA sequence of RSV or parainfluenza virus. Consequently, it is now believed that a person skilled in the art would acknowledge that claim 1, as now amended, encompasses oligonucleotides which are not antisense.

Secondly, it is respectfully resubmitted that nowhere is it taught or even suggested in Peyman *et al.* that oligonucleotides have antiviral activity against multiple viruses acting by a non-sequence complementary mode of action. Moreover, Peyman *et al.* is only enabled for

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four antisense oligonucleotides against HSV-1 in cell culture (as disclosed in column 14, lines 14-19 in Peyman). Peyman et al. only teaches how to stabilize and improve cell penetration by capping oligonucleotides (with the addition of a cap of guanine at their extremities). On the contrary, the present application teaches and claims oligonucleotides having a non-sequence complementary mode of action and that are not complementary to any portion of the genomic sequence of RSV or parainfluenza virus.

Regarding the Examiner's comment that Milligan et al. teach that sense oligonucleotides had a greater antiproliferative effect than antisense oligonucleotides, the Applicants wish to submit that said reference only describes the anti-cancer activity of antisense and sense sequence. In the context of eukaryotic cells, this means the complementary (antisense) sequence and sequence (sense) of the mRNA showed activity. A sense sequence of an mRNA as intended in Milligan et al. means the mRNA sequence itself.

Paramyxoviruses are negative RNA (-RNA) viruses. This means that the genome of the virus is a single-stranded (ss)-RNA (not translated to protein). In the cell, a ss+RNA (mRNA) is produced from the ss-RNA. In the context of paramyxoviruses, the complement of the genome (ss-RNA) is the mRNA (ss+RNA). Thus, a sequence not complementary to the genome is actually not an mRNA sequence. The mRNA sequence is the sense sequence. A sequence not complementary to the genome as claimed in the set of claim submitted herewith is not a sense sequence as taught in Milligan et al. Since a sense sequence of an mRNA as intended in Milligan et al. means the sequence itself, it is believed that the reference of Milligan et al., alone or in combination with Peyman et al., does not render obvious the claims submitted herewith.

Thus, a person skilled in the art would acknowledged that:

-in Milligan and in the field of antisense:

Antisense = a sequence complementary to mRNA  
Sense = a mRNA sequence;

-in Paramyxoviruses:

-RNA = genome  
+RNA = mRNA  
Sense sequence = mRNA sequence.

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A person skilled in the art would have no incentive to combine the teaching found in *Peyman et al.* with the teaching found in *Milligan et al.* in order to practice the present invention. Reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

It is submitted, therefore, that the claims are now in condition for allowance. Reconsideration of the Examiner's rejections is respectfully requested. Allowance of claims 1, 2, 14, 17, 18, 21, 23, 27-32 and 38-42 at an early date is solicited.

No additional fees are believed to be necessitated by this amendment. Should this be in error, authorization is hereby given to charge Deposit Account No. 19-5113 for any underpayment or to credit any overpayment.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application can be expedited.

Respectfully,

Date: February 19, 2008

By: /Christian Cawthorn/

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Enc. Petition for extension of time